Remarks and Arguments

Claims 1-20, 25-27 and 29-34 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,436,635 ("Fu"). The examiner has repeated his rejection following the applicants' last response, in which certain arguments were made in an attempt to clarify the differences between the claimed invention and the cited prior art. In a response to the applicants' arguments, the examiner states that Fu teaches the use of covalent bonds for immobilization of probes which are cleavable using photo cleavage, and cites column 17, lines 30-33 of Fu at which it is stated that: "[n]ucleic acids may be attached to the solid support by a photocleavable bond, an electrostatic bond, a disulfide bond, a peptide bond, a diester bond, or a combination of these sorts of bonds." The examiner then points out that some of these are covalent bonds, and argues that Fu therefore anticipates the claimed invention. After review, it is apparent that applicant's last response did not sufficiently identify the differences between Fu and the present invention.

The present invention and Fu both describe methods for analysis of DNA through molecular reaction performed on solid phase coupled oligonucleotide probes, followed by mass spectrometric measurement. However, there are fundamental differences between the two methods. In the method of Fu, oligonucleotide probe strands are immobilized at a surface and target sequences are then somehow connected to the probes. Indeed, a number of embodiments for connecting the target sequences to the probes are described, for example, in column 6, line 52 through column 8, line 8. However, in each of these embodiments, the reporter oligonucleotides, which are later detected mass spectrometrically, always include the target sequences. This is in distinct contrast to the present invention, in which the probes are modified based on the target sequences, and serve as the reporter oligonucleotides themselves.

The various embodiments of Fu involve different manners of attaching a target sequence to a fixed probe. Ultimately, however, the result is a probe with a target sequence either hybridized directly to it, or a probe hybridized to a sequence complementary to the target sequence, to which the target sequence is, in turn,

hybridized. The resulting "target array" is then subjected to analysis through any of a number of methods, including mass spectrometry. The probes may be attached to the solid support by covalent bonds (column 17, lines 12-25), and cleavable bonds may also be used, including photocleavable bonds (column 17, lines 30-33). The elements of the target array may then be analyzed by mass spectrometry (column 18, lines 16-18). However, it is the hybridized target strand that carries the genetic information and not the probe itself. As such, the immobilized strand is *not* the subject of the analysis.

In contrast with Fu, the present invention teaches a template-dependent modification of an oligonucleotide probes that are covalently attached to the solid support. Each probe contains a reactant for covalent attachment, the probe oligonucleotide and a photocleavable building block. All of the modification reactions (primer elongation or template dependent ligation) are performed on the single stranded probes, yielding defined reaction products containing the allele-specific information with a specific molecular mass. That is, *it is the probes themselves* that carry the genetic information to be detected by mass spectrometry. Through the primer extension or ligation steps, the probe itself is modified to reflect the specifics of the target strand. This allows the probes to be purified using denaturing conditions or materials without losing the relevant genetic information.

The claims of the present application each include limitations specifically directed to the unique aspects of the invention. Independent Claim 1 recites a method for analysis of a genetic sample, and specifically for determining the information contained in a set of target sequences. The claim further recites using a chip with spatially separated locations each containing a photocleavable oligonucleotide probe for a target sequence to be investigated. The probes are stated as being covalently bound to the surface. Step (3) of the claim then recites modifying the oligonucleotide probes "so that information under investigation is transferred from the target sequences of the templates to the probes." The probes are then cleaved from the chip surface and the sequence information is extracted from the mass measurements of the probes.

Nowhere in Fu is there any suggestion whatsoever of transferring the information under investigation from the target sequences to the probes so as to allow the sequence information to be extracted from mass measurements of the probes themselves. As this is clearly recited in applicants' Claim 1, this claim is believed to be properly allowable over the Fu prior art. Claims 2-20, 25-27 and 29-34 each depend ultimately from Claim 1, and each of these claims is therefore equally unsuggested by the cited prior art. Reconsideration of Claim 1-20, 25-27 and 29-34 under this ground for rejection is respectfully requested.

Claims 21-24 were rejected under 35 U.S.C. §103(a) as being obvious over Fu in view of U.S. Patent No. 6,355,431 ("Chee"). In making this rejection, the examiner has apparently cited Fu for the same reason as provided in the rejection based on the Fu reference alone. He adds Chee as showing "endonucleolytic cleavage using double strand-specific nuclease RNAseH when there is perfect base pairing, leading to detection of mismatch and the oligonucleotide probe contains at least one ribonucleotide."

Chee describes methods for detection and quantification of products of nucleic acid amplification reactions, using bead arrays for detection of the amplification products. To this end, Chee makes use of a primer nucleic acid that is hybridized to a target sequence to form a hybridization complex. This complex is then contacted with an enzyme for the synthesis of a modified primer nucleic acid equipped with a detectable label. The unreacted primers are removed and the hybridization complex containing at least one ribonucleotide is disassociated using double-strand specific ribonucleases. However, there is nothing in the combination of Fu and Chee that is any more suggestive of applicants' claimed invention than Fu alone. There is no suggestion of modifying covalently-bonded probes so as to transfer information to them from target sequences. Since this is clearly recited in Claim 1, from which Claims 21-24 depend, these dependent claims are likewise unsuggested by the cited prior art. Reconsideration of Claims 21-24 under this ground for rejection is respectfully requested.

Claim 28 was rejected under 35 U.S.C. §103(a) as being obvious over Fu in view of U.S. Patent No. 6,307,039 ("Southern"). In making this rejection, the examiner has apparently cited Fu for the same reasons as provided in the rejection based on Fu alone. To this is added Southern, which is cited for showing the use of a photocleavage site consisting of an o-nitrobenzyl residue. However, without commenting at length on the Southern reference, it is noted that the combination of Fu and Southern is no more suggestive of the applicants' claimed invention than the Fu reference alone. As discussed above, Claim 1 clearly recites a method that includes modifying covalently-bonded probes so as to transfer information to them from target sequences. Nowhere in the combination of Fu and Southern is there any suggestion of a method as recited in Claim 1. Since Claim 28 depends ultimately from Claim 1, this claim is equally unsuggested by the cited prior art. Reconsideration of Claim 28 under this ground for rejection is respectfully requested.

For the reasons provided above, the claims in their current form are believed to be properly allowable over the prior art of record, and their reconsideration and allowance is thereby respectfully requested. If it is believed that a telephone conference will help expedite prosecution of the application, the examiner is invited to call the undersigned. The Commissioner is hereby authorized to charge any additional fees due for the filing of this paper to applicants' attorneys' Deposit Account No. 02-3038.

Respectfully submitted

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